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James A. Williams

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EXAMINER

PORTNER, VIRGINIA ALLEN

ART UNIT

PAPER NUMBER

1645

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/727,898

Applicant(s)

WILLIAMS, JAMES A.

Examiner

Ginny Portner

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 25-36 is/are rejected.
- 7) ☒ Claim(s) 32-33 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/4/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 25-36 are pending. Claims 1-24 have been canceled.

Information Disclosure Statement

1. The information disclosure statement filed December 4, 2003 has been considered.

Claim Objections

8. Claims 32-33 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 32-33 recite process steps of "released from the cell" and "is isolated", respectively and depend from claim 25 which is directed to a composition of "A soluble botulinum toxin in a host cell"; claims 32-33 either do not further limiting the claimed composition of claim 25 by reciting a process step, which does not change or modify the claimed composition, or based upon another reading of the claims, broaden the scope of claim 25 from which they depend as the composition no longer requires the presence of the host cell, and therefore are not further limiting of claim 25.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Art Unit: 1645

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 25-36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. **5,919,665**. Although the conflicting claims are not identical, they are not patentably distinct from each other because : (Instant claims 25-31) the allowed species of claims 1-5 and 10 anticipate the instantly claimed genus of Clostridium botulinum toxin proteins together with a non-toxin protein sequence, which is a polyhistidine tag and the allowed claims are directed to a species of invention of the instantly claimed genus of botulinum toxins, wherein the allowed species is directed to a fusion protein that comprises SEQ ID NO 23 and 28 that is fused together with a non-toxin protein sequence and the instantly claimed invention is not claimed to be a fusion protein but is a recombinant botulinum toxin that comprises SEQ ID NO 28, along with a non-toxin protein sequence which is not required to be fused together with recombinant botulinum toxin, and therefore may be conjugated or linked by other means other than that defined by the recitation of "fusion protein". The allowed species anticipates the instantly claimed genus of botulinum toxins. SEQ ID NO 23 recited in allowed claims 2 defines the claimed protein to comprise Botulinum toxin A C-terminal fragment, SEQ ID NO 23 and allowed claim 3 defines the soluble fusion protein of claim 1 to include a poly-histidine tract which is SEQ ID NO 26 (allowed claim 4). The allowed species anticipates the instantly claimed genus. The claimed genus is obvious over the allowed species. Instant claims 25, 32-36 are anticipated by allowed claims 6-9 are

Art Unit: 1645

directed to a host cell that comprises at least a portion of a Clostridium botulinum toxin type A protein, the protein being expressed and soluble and evidencing the sequence represented by SEQ ID NO 28. The allowed species anticipates the instantly claimed genus of compositions.

2. Claims 25-29 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-59, 62-63 of copending Application No. 10/271,012. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims compositions of botulinum toxin portions that are fusion proteins, but claim a species of the instantly claimed genus, specifically type B or E toxin together with a polyhistidine tract. The copending species obviated the instantly claimed genus of soluble portions of a botulinum toxin..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 25-29 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-27 of copending Application No. 10/729,039. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims compositions of botulinum toxin portions that are fusion proteins, but claim a species of the instantly claimed genus, specifically type B together with type A receptor binding domain and a polyhistidine tract. The copending species obviated the instantly claimed genus of soluble portions of a

Art Unit: 1645

botulinum toxin. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 25-29 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-32 of copending Application No. 11/001,241. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims compositions of botulinum toxin portions that are fusion proteins, but claim a species (SEQ ID NO 23) of the instantly claimed genus. The copending species obviated the instantly claimed genus of soluble portions of a botulinum toxin. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5.

Claim Rejections - 35 USC § 112

9. Claims 25, 28, 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The term "soluble" in claim 25 is a relative term which renders the claim indefinite. The term "soluble" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. What is the solvent in which the soluble botulinum toxin must be soluble; how soluble must it be? While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The

Art Unit: 1645

claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed and defines the botulinum toxin to be “soluble”.

11. Claims 25 and 31 are directed to “A soluble portion of a botulinum toxin” (claim 25), that is isolated (claim 31), so what value-added does the recitation of a process step provide to structurally or functionally define the botulinum toxin claimed. What are the distinguishable characteristics between the naturally occurring botulinum toxin and one that can be recombinantly expressed? While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. Clarification is requested.

12. Claim 28 recites the phrase “the botulinum toxin of claim 25 including a non-toxin protein sequence”. The composition claimed in claim 25 from which claim 28 depends already comprises a “non-toxin protein sequence” defined by the “host cell” which comprises “non-toxin” protein sequences. How is claim 28 further limiting of the composition of claim 25 based upon the components recited in claim 25 already? Claim 28 should recite ----- wherein said botulinum toxin further comprises --- or an equivalent phrase to clearly define what the additional non-toxin protein sequence refers.

13. Claim 31 is directed to a composition in which “the botulinum toxin is isolated”; what is the botulinum toxin isolated from if it is in a host cell, as defined in claim 25, from which claim 31 depends? The claim limitations of claim 31 are not in agreement with the claim limitations of claim 25 from which it depends. What is claimed is not a method/process of purifying a

Art Unit: 1645

recombinant protein, but a composition of botulinum toxin. Clarification of how claim 31 is further limiting, and what the botulinum toxin is isolated from ?

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

3. Claims 25-29 and 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Schantz et al (1992).

23. (Instant claims 25-27 and 30-31) Schantz et al disclose a soluble botulinum toxin A that is isolated (see page 82, col. 2, paragraph 3, middle of paragraph). Schantz et al disclose isolated type A botulinum toxin in crystalline form, formulated for injection into a cell (see page 89, column 2, paragraph 5) and is therefore released from the cell and isolated.

24. (Instant claims 28-29) comprises a poly-histidine motif sequence in the H chain, the non-toxic protein chain of the toxin light and heavy chain complex (see page 88, col. 2, paragraph 2: The BoNT/A contains 6 histidines residues). The presence of type-A botulinum toxin has been

Art Unit: 1645

found associated with non-toxin protein sequences as a complex in “spent cultures (see page 87, col. 1, paragraph 5)” and contains at least two nontoxic proteins (see page 88, column 2, paragraph 4, top half of paragraph) . The botulinum toxin was also combined with bovine serum albumin into a composition; the resulting composition (see page 83, col. 2, paragraph 2, top half of paragraph) “including a non-toxin protein sequence (Instant claim 28)”.

The DNA coding region for the light chain of botulinum toxin A was cloned into a plasmid “pKN25”, which resulted in translation of the toxin protein of botulinum toxin A in a soluble form in a cell lysate.

25. Inherently the reference anticipates the instantly claimed invention, as no structural differences are set forth to differentiate a recombinantly expressed type A botulinum toxin A from that naturally produce, isolated type A botulinum toxin produced by a *Clostridium* host cell.

4. Claims 25-28, 30-31, 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Mochida et al (1990) as evidenced by Ledoux et al (1994).

Mochida et al disclose the instantly claimed invention directed to a recombinantly produced botulinum neurotoxin, wherein the neurotoxin is Toxin-A, and exists in solution in the cytoplasm of the host cell (see Materials and Methods, pages 7844-7845, Figure 1, 2 ; page 7846, col. 2, paragraph 3 ; Figure 4, page 7847), and also comprises a non-toxin protein sequence (see page 7845, col. 1, paragraph 2 “the corresponding deletion mutant, designated pBNlexo904, encoded a polypeptide that contained a Pro-Leu-Ala peptide sequence instead of the carboxyl terminal Lysine of the authentic light chain of BoNT/A.”. The Pro-Leu-Ala sequence being a non-toxin protein sequence. Mochida et al injected isolated botulinum toxin type A polypeptides into the

Art Unit: 1645

aqueous environment of the host cells (Figure 4). The host cell of Mochida, S et al (1990) being *Aplysia* neurons in which the botulinum neurotoxin was expressed recombinantly.

Ledoux et al provide evidence that *Clostridium botulinum* neurotoxins are naturally soluble in an aqueous solution (see entire abstract).

Inherently Mochida et al anticipates the instantly claimed invention.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594
2. Inherently the reference anticipates the now claimed invention. *Atlas Powder Co. v IRECA*, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. The Court further held that the same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art."
6. Claims 25, 27, 32-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Binz et al (1990) as evidenced by Ledoux et al (1994).
7. Binz et al (1990) disclose purified Botulinum toxin A (see page 9154, col. 2, paragraph 2, in 100 mM sodium phosphate), is expressed (translated) from a monocistronic mRNA (see Binz et al, page 9157, col. 2, paragraph 1, last 2 lines), and therefore would be a single chain polypeptide.
8. What is now claimed is a product by process claim directed to botulinum toxin, which can be anticipated by botulinum toxin produced by a different process that produces the same or equivalent product. No evidence has been submitted to show that what is now claimed

Art Unit: 1645

botulinum toxin structurally differs from the naturally isolated and purified botulinum toxin or the recombinantly produced botulinum toxin produced by Binz et al (see Figure 1). The light chain toxin of botulinum toxin type A was expressed as a soluble, single chain polypeptide in Binz et al, or the native toxin expressed as a single chain polypeptide was obtained from Botulinum toxin A and combined with sodium phosphate (Binz et al, page 9154, col. 2, paragraph 2, line 4) .

Additionally, Binz et discloses (page 9153, right column) that “The toxins are produced as single-chain polypeptides (Mr~150,000)” and are “proteolytically processed into two subunits upon release from the organism (page 9153, right column)”. Binz et al discloses the single chain polypeptides evidence a relative molecular weight of about 150,000 (see page 9153, col. 2, top half of first paragraph) and contain both the toxin and receptor binding functionalities (see abstract, Binz et al, lines 4-6). Binz et al anticipate the instantly claimed invention as now claimed.

5. Claims 25-27, 34-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Romanos et al (1991, reference on Applicant's USPTO 1449) as evidenced by Atassi et al (1999).

Romanos et al disclose the instantly claimed invention directed to an isolated recombinant host cell, specifically *Pichia pastoris* (see page 1466, col. 1, last paragraph), wherein the *P. pastoris* host cell expressed the recombinant nucleic acid and produced in the recombinant fragment C that comprises at least one immunogenic epitope. While the expressed recombinant fragment C was a *Clostridia* toxin portion of a toxin, specifically tetanus toxin, the expressed

Art Unit: 1645

portion comprised a portion of botulinum toxin type A, heavy chain C-fragments comprise an amino acid sequence, wherein tetanus toxin shares conserved amino acid sequences that are also inherently immunogenic (see Atassi et al, Table 5, page 249 provides evidence that the conserved amino acids comprise at least one epitope) and present in botulinum toxin A.

Atassi et al, pages 248 and 249, Figure 14 and Table 5, provides evidence that shows Te (tetanus toxin) and botulinum toxin type A, heavy chain C-fragments comprise an conserved/common amino acid sequence portion.

Romanos et al inherently anticipates the instantly claimed invention as now claimed in light of evidence provided by Atassi et al showing tetanus toxin and botulinum toxin type A to share conserved immunogenic amino acid epitopes within the heavy chain fragment-C domain, the amino acids being an amino acid sequence of a botulinum toxin .

6. Claims 25-28, 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by LaPenotiere et al (1993; presented in May 1992 International Conference on Botulinum, Tetanus Neurotoxins, reference cited on Applicant's USPTO 1449) in light of Ledoux et al (1994, reference of record) who teaches botulinum toxin to be a water soluble protein.

LaPenotiere et al disclose the instantly claimed invention directed to:

- a recombinant (LaPenotier et al, "molecular engineered", title)
- botulinum (see title) toxin (neurotoxin)
- protein (Hc polypeptide fused to E.coli maltose binding protein, see LaPenotiere et al, abstract), wherein
- the soluble C-terminal portion (in light of Ledoux et al who teaches botulinum toxin is inherently a water soluble protein) is

Art Unit: 1645

- produced by a process using an aerobic bacteria (E.coli grows in the presence of oxygen, see E.coli expression, abstract),
- the polypeptide being expressed as a single fusion protein polypeptide in a bacteria, that is free of neurotoxin complex proteins, as only the Hc portion was recombinantly expressed in E.coli, wherein the toxin is in a solution ("dilutions", see page 464, paragraph 3; "culture medium", and "resuspended" see page 464, paragraph 4; in complete Freund's (see page 465, paragraph 2).

The C-terminal botulinum toxin recombinant protein of LaPenotiere et al inherently anticipates the instantly claimed invention.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594
2. Inherently the reference anticipates the now claimed invention. *Atlas Powder Co. V IRECA*, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. AThe Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.
7. Claims 25-28,30-33are rejected under 35 U.S.C. 102(e) as being anticipated by Dolly et al (US Pat. 6,203,794, effective filling date May 31, 1994) as evidenced by Ledoux et al (1994).

Art Unit: 1645

Dolly et al disclose the instant claimed invention directed to a recombinant botulinum neurotoxin (see Dolly et al, col. 2, lines 25-36), wherein the botulinum toxin is botulinum toxin A, B, C, D, E, F and G (see Dolly et al, col. 7, lines 18-30; col. 41, claims 2-3).

(Instant claims 25-27) The botulinum toxin comprises a light chain portion (see Dolly et al, col. 8, line 2; see Dolly et al, claims 1-3; col. 24, lines 62-65; Example 15), a heavy chain targeting portion and an internalizable portion (see Dolly et al, claim 4, and col. 5, lines 12-14) which are equivalent portions to the C-terminal and N-terminal functions of a botulinum heavy chain. The botulinum toxin is claimed as a pharmaceutical composition (see Dolly et al claim 4) and is in solution with a pharmaceutically acceptable excipient (see Dolly et al, col. 41, lines 66-67).

(Instant claim 28, 30-33) The recombinant botulinum toxin is expressed using a maltose binding protein (see col. 17, lines 29-39) expression vector (see Dolly et al, for example: col. 3, lines 54-66) and would therefore evidence a specific solubility conferred by the expression vector fusion protein. The botulinum toxin is disclosed to be mutated through the addition of a non-toxin sequence, specifically a "cysteine" at the N-terminal of the light chain (see Dolly et al, col. 12, lines 55-61). An additional embodiment disclosed is the expression of the recombinant light chain as a fusion protein that comprises "a non-toxin protein sequence" that is cleavable by Factor Xa (see Dolly et al col. 28, lines 59-64; figure 1A) or is a GST fusion protein (see Dolly et al, Example 21, col. 31).

Dolly et al anticipates the instantly claimed invention as now claimed, in light of the evidence Ledoux et al provides that defines botulinum toxins to be water soluble proteins (see abstract, page 1095).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over LaPenotiere et al, (1993) as applied to claims 25-28, 30-33 above, in view of Williams et al (US Pat. 5,601,823, different inventive entity).

9. See discussion of LaPenotiere et al above. LaPenotiere et al teaches and produces a recombinant clostridium botulinum toxin C-terminal fragment protein that is expressed in an aerobic bacteria and is produced as a single polypeptide chain, wherein the single polypeptide chain comprises an additional maltose binding protein polypeptide sequence coupled to the C-terminal portion of the botulinum toxin but differs from the instantly claimed invention by failing to show the additional coupled polypeptide to be a polyhistidine tract.

10. Williams et al teaches the production of recombinantly produced clostridium(see col. 8, lines 13-22, lines 59-67) which includes botulinum and difficile toxins (see col. 3, lines 25-29)) as single chain polypeptides either through coupling the toxin to a maltose binding protein polypeptide or to a polyhistidine tract polypeptide (see col. 35, lines 26-49, Example 11) in an analogous art for the purpose of producing large quantities of recombinant toxins for formulation

Art Unit: 1645

of vaccines and generation of neutralizing antibodies induced to the recombinant clostridium toxins.

11. It would have been obvious to the person of ordinary skill at the time the invention was made to modify the recombinant polypeptide of LaPenotiere et al that comprised a maltose binding protein non-toxin protein with the polyhistidine tract of Williams et al because Williams et al teaches and shows the successful production of recombinant clostridium toxins and teaches prokaryotic expression systems for the attainment of recombinant Clostridial toxins through expression of single polypeptide chains, wherein the single polypeptide chains will bind to a ligand containing column to aid in protein isolation and purification, the polypeptides including either a maltose binding protein or a polyhistidine tract polypeptide tag (pET16b) (see Example 11, column 35), and these methods serve to define means for attainment of high levels of recombinant toxin.

12. The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a botulinum C-terminal portion recombinant protein that comprises a polyhistidine tract utilizing the expression system of Williams et al because both LaPenotiere et al and Williams teach the utilization of maltose binding protein expression system for the recombinant expression of Clostridial toxins and Williams also successfully showed the recombinant expression of a Clostridial toxin using a polyhistidine tract polypeptide which provides the advantage of attaching the polypeptide polyhistidine tract either at the C-terminal end (pET23a-c) or the N-terminal end (pET16b) (see Example 11, col. 35, lines 26-49) of the Clostridial polypeptide depending on the preferred location of the non-toxin polyhistidine tract

Art Unit: 1645

polypeptide. In the absence of a showing of unexpected results, LePenotiere et al in view of Williams et al obviate the instantly claimed invention.

9. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dolly et al (US Pat. 6,203,794) as applied to claims 25-28 and 30-33 above, in view of Crowe et al (1994).

See discussion of Dolly et al above. Dolly et al teach, show and provide guidance for producing a recombinant botulinum toxin (see Examples 12-13), wherein the recombinant botulinum toxin is expressed as a fusion protein together with a non-toxin protein sequence (see col. 24-26). Dolly et al differs from the instantly claimed invention by failing to show the non-toxin protein sequence to be a polyhistidine tag.

Crowe et al teach a polyhistidine (6xhis) recombinant protein expression and purification system in an analogous art for the purpose of defining a superior technique for not only obtaining recombinant proteins, but recombinant proteins that are readily purified as well.

It would have been prima face obvious to the person of ordinary skill in the art at the time the invention was made to modify the cloning system of Dolly et al with the cloning system of Crowe et al because Crowe et al teaches a cloning system that is superior to other known systems for producing recombinant proteins.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining an isolated polyhistidine botulinum toxin fusion protein because Crowe et al teaches that the polyhistidine cloning systems utilizes an nickel affinity purification step that readily isolated and purifies the

Art Unit: 1645

expressed recombinant protein from other bacterial host cell proteins (see Descriptors of reference).

Conclusion

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

11. Murphy et al (US Pat. 5,965,406 or 6,022,950) discloses a plurality of embodiments, and not just the two part protein cited at col. 2, a three part recombinant toxin, specifically a recombinant botulinum toxin that is a hybrid toxin that includes an enzymatically active light chain botulinum toxin (see Murphy '406, claims 12 and 21).

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, A. Mark Navarro can be reached on (571) 272-0861. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1645

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Vgp
September 29, 2006



MARK NAVARRO
PRIMARY EXAMINER